REMARKS

A. Regarding the Amendments

By the present amendment, claims 67 and 91 have been amended to more particularly define Applicant's invention. Claims 68, 69, 71, 72, and 92-94 have been canceled without prejudice. As amended, the claims are fully supported by the specification and the original claims and add no new matter. In particular, the following limitation has been added to claims 67 and 91:

> "mitochondrial disorder is selected from a group consisting of mitochondrial renal tubular acidosis, multiple mitochondrial deletion syndrome, Leigh syndrome, lactic acidemia, 3-hydroxybutyric acidemia, encephalomyopathy, 1+proteinuria, pyruvate dehydrogenase deficiency, complex I deficiency, complex IV deficiency, aminoaciduria, hydroxyprolinuria, ataxia, and MARIAHS syndrome."

The limitation is fully supported by the original specification. For example, the treatment of various mitochondrial disorders is disclosed in the following portions of the original specification:

mitochondrial renal tubular acidosis – Example 1 (page 14, lines 7-8);

multiple mitochondrial deletion syndrome – Example 4 (page 17, line 23);

Leigh syndrome – Example 1 (page 14, lines 15 and 17), and Example 5 (page 18, line 16);

lactic academia – Example 1 (page 14, lines 17 and 20-21);

3-hydroxybutyric academia – Example 1 (page 14, line 20);

encephalomyopathy – Example 1 (page 14, line 21), and Example 3 (page 16, line 22);

1+proteinuria – Example 1 (page 14, lines 17-18);

pyruvate dehydrogenase deficiency – Example 1 (page 14, line 18);

complex I deficiency – Example 1 (page 14, line 12);

complex IV deficiency – Example 1 (page 14, lines 15-16);

aminoaciduria – Example 1 (page 14, line 14);

hydroxyprolinuria – Example 1 (page 14, line 14);

ataxia – Example 3 (page 16, line 22); and

MARIAHS syndrome – Example 2 (page 15, line 20).

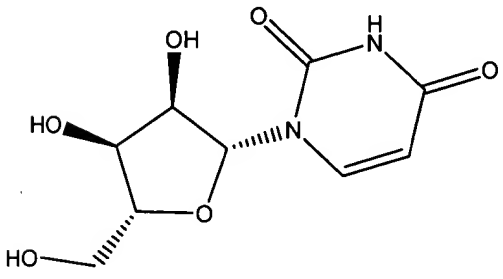
Upon entry of this amendment, claims 67, 70, and 73-91 remain under consideration.

B. Rejection Under 35 U.S.C. § 112

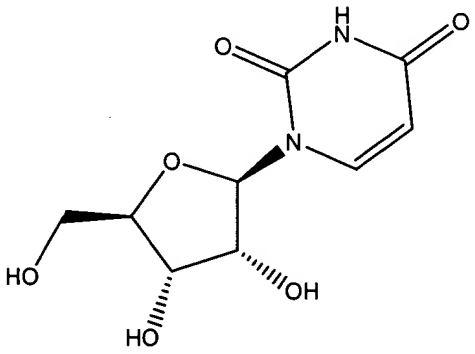
Claims 67-94 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention (the written description requirement) (page 2 of the Office Action). The claims have been also rejected as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (the enablement requirement) (page 2, lines 18-21 of the Office Action).

With regard to the written description rejection, use of uridine is disclosed in the original specification. For example, Example 2 describes treatment of a child suffering from MARIAHS syndrome (page 15, line 19 through page 16, line 17). The treatment included two stages. At first stage, the child was treated with uridine for 1.5 years, before the treatment with triacetyluridine commenced (page 16, lines 1-3). Additionally, the specification describes "supplementing uridine," where administration of triacetyluridine is merely one example of a compound that can be used for such "supplementing" (page 4, line 17). Using other uridine-based compounds, including pure uridine itself, is not excluded. Thus, using uridine as a part of overall course of treatment has been clearly described. The amended Formula (I) provided in claims 67 and 91 is directed to uridine expressed as a chemical structure.

The Applicant further respectfully points out that the compound having generic Formula (I) shown in claims 67 and 91, is intended to broadly illustrate not only uridine but also 1-β-D-ribofuranosyluracil, which are the stereochemical isomers the structures of which are shown below. Those having ordinary skill in the art know that "uridine" is a generic traditional name covering both. Therefore, when the use of uridine is disclosed, the use of 1-β-D-ribofuranosyluracil is also implicitly disclosed.



uridine



1-β-D-ribofuranosyluracil

With respect to the lack of enablement rejection, claims 67 and 91 have been amended and now recite particular disorders that can be treated. As pointed out above, Examples 1-5 provide clear guidelines on how the method can be practiced.

Accordingly, the Applicant respectfully submits that the specification provides adequate support for claims 67 and 91 and that at the time of filing the Applicant was in possession of the method for treating mitochondrial disorders utilizing these compounds. The Applicant respectfully submits that the claims are now properly enabled. Reconsideration and withdrawal of the rejection are respectfully requested.

C. Rejection Under 35 U.S.C. § 102 (a)

Claims 68 and 92 have been rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Loffler et al., Dihydroorotat-Ubiquinone Oxidoreductase Links Mitochondria In the Biosynthesis Of Pyrimidine Nucleotides, *Molecular and Cellular Biochemistry*, 174: 125–129 (1997) (page 5, line 19 of the Office Action). This rejection is respectfully traversed. Claims 68 and 92 have been canceled and the subject matter rejected by the Examiner has been incorporated into claims 67 and 91.

The Applicant respectfully provides a Declaration by the inventor under 37 C.F.R. § 1.131. As stated in the Declaration, this invention was conceived of and reduced to practice prior to the publication date of Loffler et al. The Declaration is supported by the following evidence. Copies of relevant pages from the inventor's laboratory book attached as Exhibit A demonstrate that the invention was indeed reduced to practice. A declaration by Dr. William Nyhan attached as Exhibit B clearly demonstrates that the invention was conceived prior to the publication date of Loffler et al. because the inventor confidentially discussed the concept on a date preceding the publication date of Loffler et al. An article published in ctnow.com a copy of which is attached as Exhibit C further illustrates that the inventor had reduced the invention to practice prior to the publication date of Loffler et al. Accordingly, in accordance with MPEP §§ 706.02(b) and 715, the Loffler et al. reference is considered antedated.

In addition, Loffler et al. fail to disclose uridine-based treatment of various disorders recited in the amended claims 67 and 91. What Loffler et al. do describe is treatment of megaloblastosis, leucopenia, fatigue, weakness, immune deficiencies, and physical and intellectual retardation " (see, page 128, col. 2, lines 8-10). However, they question whether "uridine treatment could improve the general well-being of patients suffering from mitochondrial disorders" (see, page 128, col. 2, lines 18-20) since "a dose of 100 mg uridine/kg body weight per day was necessary for these patients," which is presumably too large a dose (see, page 128, col. 2, lines 14-15). Loffler leave the question concerning using uridine for future discussion (see, page 128, col. 2, lines 20-21) and never teach the uridine treatment that is claimed here.

Therefore, the Loffler et al. reference fails to disclose every element of claims 67 and 91, and, accordingly, is not a proper prior art reference under 35 U.S.C. § 102(a). Reconsideration and withdrawal of the rejection are respectfully requested.

D. Rejection Under 35 U.S.C. § 103 (a)

Claims 67-80 and 88-94 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,472,378 to von Borstel (page 5, lines 8-9 of the Office Action). This rejection is respectfully traversed. Claims 68, 69, 71, 72, and 92-94 have been canceled. Therefore, only claims 67, 70, 73-80, and 88-91 have to be considered for the purposes of this rejection.

It is submitted that von Borstel can qualify as a prior art reference only under 35 U.S.C. § 102(a) or § 102(e). Therefore, the above-described Declaration by the inventor under 37 C.F.R. § 1.131 properly antedates this reference.

Accordingly, it is respectfully submitted that claims 67 and 91 are patentable over von Borstel. Claims 70, 73-80, and 88-90 depend, directly or indirectly, on claim 67, and are allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

A check No.575583 in the amount $510.00 to cover the fee for three months extension is attached herewith. No other fees are believed due in connection with this Response. In the event that an additional fee is due, the Commissioner is hereby authorized to charge any amounts required by this filing, or credit any overpayment, to Deposit Account No. 07-1896.

Respectfully submitted,

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HEALTH

Learning From A Child

By WILLIAM HATHAWAY
The Hartford Courant

April 10, 2001

Cristin Murphy-Zink of Simsbury was 2 years old before a doctor told her parents their daughter's seizures and developmental delays were caused by a malfunction in her mitochondria - essentially her cellular power packs.

Her parents also learned that in most cases doctors and scientists have not found ways to treat failures of the mitochondria, ancient bacterial hitchhikers that are one of life's primary energy suppliers.

Mara Mirko photo

Cristin Murphy-Zink has been developing normally since she started taking an experimental medicine called uridine to treat a rare mitochondrial disorder.

While Cristin's condition is relatively rare, scientists say studying mitochondrial diseases in children has helped reveal the role mitochondria may play in common adult ailments such as heart disease, diabetes, cancer and Alzheimer's.

Some researchers even believe that damage to the mitochondria, the tiny organelles in each of our cells that convert food and oxygen into energy, causes the ravages of age.

"Everybody in the field feels like we are seeing just the tip of the iceberg," said Dr. Robert Naviaux, director of the mitochrondrial and metabolic disease center at the University of California at San Diego, who began to see Cristin when she was about 18 months old.

Mara Mirko photo

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"But the methods of diagnosis are still in their infancy. Once we improve those, I believe we will find [mitochondrial disorders] affect a much larger group of patients."

For the first two years of Cristin's life, Eileen Murphy and John Zink never got an explanation from San Diego-area doctors that satisfied them about their daughter's condition.

"She never really thrived after she was born," said Murphy, who had moved from Norwalk to San Diego after Cristin was born.

Cristin often vomited after eating and had to be fed through tubes implanted in her stomach. She regularly had violent seizures, sending her parents rushing her to the hospital or scrambling to give her valium and oxygen. That would stop the convulsions, which caused Cristin's body to contort and her eyes to roll back.

She didn't walk until she was 3 or talk until she was 4. She was variously diagnosed with cerebral palsy, multiple sclerosis and Angelman's Syndrome, a developmental disorder.

Those diagnoses never made sense to Murphy and her husband, who kept pushing doctors to run more tests. Before Cristin's second birthday, Murphy took her daughter to see Naviaux, who months later said he thought Cristin had an unspecified mitochondrial disorder.

Murphy, an engineer trained at Massachusetts Institute of Technology, quit her job at Hewlett Packard to volunteer in Naviaux's laboratory in order to learn more about the disease - and potential treatments.

There are about three dozen identified mitochondrial diseases, many of which are inherited from the mother. Mitochondria have their own DNA, a vestige of an ancient past when they existed as free-living bacteria. Most scientists believe the mitochondria merged with their host cells long ago, creating a sort of cellular battery that also helps produce the raw material of DNA and RNA, the genetic code of life.

Mitochondrial diseases can affect any organ of the body and can mimic other diseases. Current diagnostic tests miss many cases, and the most accurate test is a painful muscle biopsy. Mitochondrial diseases also have been implicated in many cases of Sudden Infant Death Syndrome.

The diseases are relatively rare, affecting about one of 4,000 people. Some diseases can be treated by dietary change, but no treatments exist for most of the diseases.

The oft-overlooked mitochondria also are thought to play a role in the development of many common diseases. For instance, mutations in mitochondria have been linked with the body's inability to order the destruction of damaged

cells, a failure that can lead to the development of cancer.

"It makes sense that defects and problems in the processing of oxygen would lead to different organ systems' suffering," said Michael Brown, researcher at Emory University's Center for Molecular Medicine. "But the magnitude of the problem is just now being understood."

Brown and others at Emory are studying whether mutations in mitochondria help produce dangerous free radicals, which have been implicated in the aging process.

In his research, Naviaux also is exploring possible links between mitochondrial dysfunction and macular degeneration, the leading cause of blindness in the United States.

"I try not to overstate the case and to remain cautious, but in my heart of hearts, I really believe the study of mitochondrial disease will start a revolution in medicine," Naviaux said.

For young Cristin, now 7, the revolution may have come early. At Naviaux's urging, Cristin for the past four years has been taking an experimental medicine called uridine, a key biochemical compound that healthy mitochondria help produce. Last month, Repligen Corp., a Needham, Mass., biotechnology company, announced plans to launch human trials of a form of uridine to test its efficacy in children with mitochondrial diseases.

Her parents, who returned to Connecticut more than a year ago, say Cristin has thrived since she began taking uridine. The girl who once wouldn't speak is now a bright-eyed chatterbox. While still about two years behind her first-grade peers, Cristin is making rapid progress in school with the help of special-education teachers, Murphy said.

"Right now, her education and the rest of her life is what's most important," Eileen Murphy said.

Naviaux said cases like Cristin's can teach researchers a lot about the impact of mitochondria on overall health. "I like the aesthetic that understanding children who were born with the disease will teach us something very important about diseases adults acquire."

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